PERIPHERAL BLOOD B-CELLS AND CXCR3+ EXPRESSION IN CHRONIC HEPATITIS C VIRUS INFECTION

Arsentieva N. A. [a, b],

Elezov D. S. [a],

Kudryavtsev I. V. [c, b],

Korobova Z. R. [a, b],

Totolian A. A. [a, b]

[a] Saint Petersburg Pasteur Institute, St. Petersburg, Russian Federation.

[b] First St. Petersburg State I. Pavlov Medical University, St.Petersburg, Russian Federation.

[c] Institute of Experimental Medicine, St.Petersburg, Russian Federation.

СУБПОПУЛЯЦИИ В- И CXCR3+ В-КЛЕТОК ПЕРИФЕРИЧЕСКОЙ КРОВИ БОЛЬНЫХ ХРОНИЧЕСКИМ ВИРУСНЫМ ГЕПАТИТОМ С

Арсентьева Н. А. [1, 2],

Елезов Д. С. [1],

Кудрявцев И. В. [3, 2],

Коробова З. Р. [1, 2],

Тотолян А. А. [1, 2]

[1] ФБУН НИИ эпидемиологии и микробиологии имени Пастера, Санкт-Петербург, Россия.

[2] ФГБОУ ВО «Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова» Министерства здравоохранения Российской Федерации, Санкт-Петербург, Россия.

[3] ФГБНУ «Институт экспериментальной медицины», Санкт-Петербург, Россия.

Abstract

Hepatitis C virus (HCV) infection remains a serious global healthcare challenge, often leading to chronic disease with complications such as liver cirrhosis, hepatocellular carcinoma, and extrahepatic manifestations. According to the World Health Organization (WHO), an estimated about 50 million people lived with chronic HCV infection in 2022, highlighting the ongoing need to understand the immune mechanisms driving disease progression. HCV may evade of immunosurveillance, so that disease progression is linked to specific immune response, whereas reactivation risk after antiviral therapy exists, which together account for a need to gain understanding of underlying immune mechanisms. HCV may infect lymphocytes primarily B cells serving as a virus reservoir and result in diverse systemic complications. The current study focused on analyzing peripheral blood CXCR3+ B cells at various differentiation stages in patients with chronic HCV infection to assess a potential link to clinical and laboratory markers of disease progression. Blood samples collected from 58 patients with chronic HCV infection and 27 healthy controls were examined. When analyzing flow cytometry data, we noted a significant B cell redistribution in HCV infection compared to control samples presented as a shift towards activated mature, resting memory and 'double negative' B cells characterized by increased expression of chemokine receptor CXCR3. Flow cytometry analysis revealed no significant difference in total B-cell (CD19+) but elevated memory B-cells (CD27+CD19+) (p=0.037). CXCR3 expression peaked on memory B-cells and increased across all B-cell subsets in HCV patients (p<0.001). Redistribution toward differentiated B cell subsets— double-negative (CD38–CD27–), resting memory (CD38–CD27+), and activated mature (CD38+CD27+) B-cells was observed, with elevated CXCR3+ percentage in the latter two subsets (p=0.017 and p=0.001, respectively). HCV viral load correlated positively with CD38+ B-cells and CXCR3+ naïve/activated mature subset counts but inversely with CD38+ B1/B2/memory cell levels. Genotype 1 and advanced fibrosis (F3/cirrhosis) were associated with reduced B2 cells and increased

CXCR3+ B1/B2 subset levels. These findings suggest that chronic HCV infection drives B-cell differentiation and CXCR3-mediated recruitment to the liver, implicating CXCR3 in disease progression.

Резюме

Инфекция, вызванная вирусом гепатита С (ВГС) является серьезной глобальной проблемой здравоохранения. По данным Всемирной организации здравоохранения за 2022 год в мире около 50 миллионов человек живут с хроническим вирусным гепатитом С. Инфицирование ВГС часто приводит к хроническому течению, сопровождающемуся такими осложнениями, как цирроз печени, гепатоцеллюлярная карцинома и внепеченочные проявления. ВГС способен уклоняться от иммунной системы, прогрессирование заболевания связывают с реализацией иммунного ответа, после противовирусной терапии существует риск реинфекции, эти причины обуславливает необходимость понимания иммунных механизмов, определяющих развитие заболевания. ВГС способен инфицировать лимфоциты, в частности В-клетки, приводя к различным системным осложнениям, кроме того, В-клетки могут являться резервуаром для ВГС. Таким образом целью исследования стало изучение субпопуляций CXCR3+ В-клеток различных стадий дифференцировки в периферической крови пациентов с хроническим вирусным гепатитом С и связи субполпуляций В-клеток с клиническими и лабораторными маркерами прогрессирования заболевания. В исследовании использованы образцы крови от 58 пациентов с хроническим вирусным гепатитом С и от 27 условно здоровых лиц. Анализируя результаты проточной цитометрии, мы обнаружили значительное перераспределение субпопуляций В-лимфоцитов при хронической инфекции, вызванной ВГС по сравнению с контролем. Наблюдался сдвиг в сторону активированных зрелых, покоящихся клеток памяти и «двойных отрицательных» В-клеток. На этих клетках была повышена экспрессия хемокинового рецептора CXCR3. Не выявлено существенной разницы в общем количестве В-клеток (CD19+) по сравнению с контролем, но количество В-клеток памяти (CD27+CD19+) было повышено (p=0,037). Экспрессия CXCR3 была наиболее высокой на В-клетках памяти и повышена

во всех субпопуляциях B-клеток у пациентов с хроническим вирусным гепатитом C (p<0,001). Установлено перераспределение в сторону дифференцированных субпопуляций - дважды негативных (CD38-CD27-), покоящихся клеток памяти (CD38-CD27+) и активированных зрелых (CD38+CD27+) B-клеток. Была продемонстрирована положительная корреляция между вирусной нагрузкой и уровнем CD38+ B-лимфоцитов, а также CXCR3+ наивных/активированных зрелых субпопуляций. Клетки памяти CD38+ B1/B2 продемонстрировали отрицательную корреляцию с вирусной нагрузкой. Для генотипа 1, прогрессия фиброза (F3/цирроз была ассоциирована со снижением B2 клеток и повышенным содержанием CXCR3+ B1/B2 субпопуляций. Данные результаты предполагают, что в прогрессии HCV инфекции задействован рецептор CXCR3.

Ключевые слова: B-клетки, CXCR3, гепатит C, проточная цитометрия, вирусная нагрузка, фиброз печени.

1 **Introduction**

Hepatitis C virus (HCV) infection remains a serious problem for global healthcare. The disease is often chronic, with the development of liver cirrhosis, hepatocellular carcinoma and/or extrahepatic complications. According to World Health Organization (WHO) data, in 2022 there were 50 million HCV patients worldwide [23].

Despite being known for tropism to liver tissues, HCV replicates not only in hepatocytes, but also in various types of immune cells. HCV infects the cell through interaction with CD81 receptor on the surface of hepatocytes and B lymphocytes. Some authors suggest that B-cell virus tropism leads to various systemic complications, such as mixed cryoglobulinemia [7], rheumatoid factor production [15], lymphoproliferative disorders [24], B-cellular lymphoma [20-21]. In addition, it is likely that B-cells may act as an additional reservoir for HCV survival in the host [9]. Therefore, B lymphocytes can play a significant role in the immune aspects of chronic hepatitis C development and its complications.

Studying B-cell subsets and their role in development of infectious diseases is an object of high interest, correlating with clinical and laboratory markers of disease activity. However, subsets of peripheral B lymphocytes in chronic hepatitis C are poorly studies compared to other infections. In the classical way of B lymphocyte differentiation into subsets of B1, B2 and memory B-cells receptors CD5 and CD27 are used as markers. B2 cells (CD5–CD27–) form the main subset of B lymphocytes and play a major role in the humoral immune response. Memory B-cells expressing CD27 are more sensitive to antigen stimulation, they proliferate quickly and form plasma cells [5]. CD5-expressing B1 cells are associated with production of autoantibodies; their increase considered to be related with autoimmune pathology [10].

Another B lymphocyte differentiation scheme according to the stages of maturation is based on co-expression of CD27 and CD38 [8]. The smallest subset is

29 transitional B-cells (CD38brightCD27–). This population migrates from bone

30 marrow to secondary lymphoid organs as the earliest subset of B lymphocytes that

31 appears in peripheral blood. The largest subset is "naïve" mature B-cells

32 (CD38+CD27–) with signs both of "naïve" and mature B-cells. A subset of activated

33 mature B-cells (CD38+CD27+) can be differentiated into a subset of resting memory

34 B-cells (CD38–CD27+) or plasma cells (CD38brightCD27+). The final subset is

35 "double negative" B-cells (CD38–CD27–) with no clearly described features [12].

36 This classification allows to better characterize both stages of maturation and

37 B-cellular immune responses in chronic hepatitis C.

38 One of the most well studied chemokine receptors in HCV infection is

39 CXCR3. The expression of this chemokine receptor increases significantly on B

40 lymphocytes and, especially, on memory B-cells during chronic infection [16]. This

41 reflects migration and involvement of these cells in damaged liver tissue and their

42 participation in immunopathogenesis of chronic hepatitis C [13]. We, too, previously

43 published data on B-cellular subsets and CXCR3 expression [1]. Within our previous

44 study, we explored B1, B2 and B memory subsets between HCV infected individuals

45 and controls. We noted no statistically significant differences between these groups.

46 However, the percentage of CXCR3+ cells was higher in patients with HCV

47 infection. To further investigate these finding, we improved the gating strategy by

48 adding CD38. The use of current gating strategy based on CD27 and CD38

49 expression allows to determinate all main peripheral blood B lymphocyte subsets

50 and measure CXCR3 expression. Moreover, we added severity of liver fibrosis and

51 the viral load into analysis.

52 The purpose of this study is to investigate changes in the peripheral B and

53 CXCR3+ B-cell subsets in chronic HCV patients and explore a relationship between

54 clinical and laboratory markers of disease activity.

55 2 **Materials and Methods**

56   For this study, we used blood samples from 58 patients with chronic hepatitis

57 C infection. All patients were positive for HCV RNA, had not received antiviral

58 therapy, and were not infected with HBV and/or HIV.

59   The control group included 27 healthy donors not infected with HCV, HBV

60 and/or HIV. All participants lived in the North-West region of Russia.

61   Data acquisition was performed with flow cytometer Navios™ (Beckman

62 Coulter, USA) equipped with 488 and 638 nm diode lasers. The following

63 monoclonal antibodies (mAbs) were used with corresponding mouse IgG isotypes:

64 CD5-FITC (clone BL1A), CD38-PE (clone LS198-4-3), CD3-ECD (clone UCHT1),

65 CD27-PE/Cy7 (clone 1A4CD27), CXCR3-APC (clone G025H7), CD19-APC-

66 Alexa Fluor 700 (clone J3-119).

67   All above-mentioned mAbs were manufactured by Beckman Coulter, USA

68 except for CXCR3-APC (by BioLegend, USA). Sample preparation was performed

69 according to the standard procedure [2]. The gating strategy for the main B-cell

70 subsets was described previously [11]. We used VersaLyse lysing solution

71 (Beckman Coulter, USA) for erythrocyte lysis. At least 50000 lymphocytes were

72 analyzed in each sample. The absolute number of cells was determined using

73 FlowCount™ reagent (Beckman Coulter, USA).

74   For a study of B-cell subsets content and CXCR3 expression depending on

75 HCV genotype all patients were divided into two groups – genotype 1 (n=35) and

76 "non-1" genotype (n=23). The stage of liver fibrosis was assessed via METAVIR

77 scale (F0 - absence of fibrosis, F1 - weak fibrosis, F2 - moderate fibrosis, F3 - severe

78 fibrosis and F4 - cirrhosis) [22]. Based on fibrosis stage, patients were divided into

79 three groups: F0-F1 (n=27), F2 (n=12) and F3-F4 (n=10). All patients were tested

80 for viral load. Data were analyzed using Navios Software v.1.2 and Kaluza™ v.1.2

81 (Beckman Coulter, USA). Statistical analysis was performed using GraphPad Prizm

82 6 (GraphPad Software, USA). Data are presented as median, interquartile range (25;

83 75%), minimum and maximum values. Statistical significance between groups was

84 determined by Mann-Whitney test, differences were considered significant at p <

85 0.05. Correlations between parameters were assessed using Spearman correlation

86 analysis.

87 3 **Results**

88   The strategy of peripheral B lymphocyte subset analysis included separation

89 of B-cells from other lymphocyte subsets based on CD19 expression. Then, using

90 dot plot for a distribution of B-lymphocytes numbers of B1 (CD5 +), B2 (CD5–

91 CD27–) and B memory (CD27+) cells were determined by expression levels of CD5

92 and CD27. Based on co-expression of CD38 and CD27, we analyzed transitional

93 cells (CD38brightCD27–), "naïve" mature cells (CD38+CD27–), resting memory

94 cells (CD38–CD27+), activated mature cells (CD27+CD38+) and "double negative"

95 cells (CD38–CD27–) (Fig. 1). Expression of the chemokine receptor CXCR3 was

96 determined on a separate histogram for each subset of B-cells.

97   The total number of B-cell subsets (CD19+) in peripheral blood of HCV

98 patients was not significantly different (p=0.68) from the control group. When B

99 lymphocytes were divided into B1 (CD5+CD19+), B2 (CD5–CD27–CD19+) and B

100 memory cells (CD27+CD19+), elevated numbers of memory B-cells were seen in

101 HCV patients (p=0.037). CXCR3 expression was different among B-cell subsets in

102 both groups (Fig. 2). Memory B-cells expressed CXCR3 at high levels, whereas the

103 expression for B1 and B2 cells was comparatively less. In HCV patients, an

104 increased number of all three subsets of B-cells expressing CXCR3 (p<0.001) was

105 noted.

106   Numbers and percentages of transitional (CD38brightCD27–), "naïve" mature

107 (CD38+CD27–),   resting   memory   (CD38–CD27+),   activated   mature

108 (CD38+CD27+), "double negative" B-cells (CD38–CD27–) and subsets of these

109 cells expressing CXCR3 were determined. In HCV patients, a redistribution of B

110 lymphocyte subset composition was seen, from "naïve" resting B-cells towards more

111 differentiated subsets of "double negative", resting memory and activated mature B-

112 cells. The percentage of CXCR3+ cells was also elevated among resting memory B-
113 cells (p=0.017) and activated mature B-cells (p=0.001).

114   The content of CD38+ cells of B lymphocytes (this subset includes
115 transitional, "naïve" and activated mature B-cells) correlated with HCV viral load
116 (r=0.453; p=0.014), and the content of CD38+ cells of B1 (r=–0.401; p=0.031), B2
117 (r=–0.538; p=0.003) and memory B-cells (r=–0.403; p=0.030) inversely correlated
118 with HCV viral load. Correlations were observed also between HCV viral load and
119 the content of "double negative" B lymphocytes (CD38–CD27–) (r=0.453;
120 p=0.014), CXCR3+ B lymphocyte subsets: CXCR3+ "naïve" mature B-cells
121 (r=0.394; p=0.034) and CXCR3+ active mature B-cells (r=0.477; p=0.009).

122   Based on the HCV genotype, the group with genotype 1 there demonstrated a
123 reduced (p=0.009) percentage of B2 cells 55.57% (48.44; 59.32) compared with the
124 group of healthy donors 68.96% (59.6; 72.43).

125   In the group of HCV patients with fibrosis F0 and F1, there were increased
126 numbers of memory B subset (p=0.015) and a reduction of B2 subset (p=0.012)
127 compared with the control group. In the group of HCV patients with F3 fibrosis and
128 liver cirrhosis, an elevation of memory B-cell subset (p=0.015) and reduction of B2
129 cell subset (p=0.004) were seen compared to the HCV patients with F0 and F1
130 fibrosis. The numbers of CXCR3+ B1 and CXCR3+ B2 subsets in the group of
131 patients with F3 fibrosis and liver cirrhosis were elevated compared with the group
132 with F0 and F1 fibrosis (p=0.050; p=0.027). There was a trend towards a rise in the
133 numbers of CXCR3+ B1 and CXCR3+ B2 cells as the fibrosis progressed (Fig. 3).

134 4 **Discussion**

135   The available studies on memory B-cells in HCV patients are contradictory.
136 Our results are most consistent with the results of Rosa et al, 2005 and show an
137 increased percentage of memory B-cells in peripheral blood of HCV patients
138 compared to the control group [16]. This is also consistent with the fact that CD27+

139 B-cells are less prone to apoptosis than CD27– B-cells [14] which explains their
140 elevation in the peripheral blood. Memory B-cells are quickly activated by antigen
141 stimulation.

142   In the group of HCV patients a reduced percentage of B1 cells was noted when
143 compared to the total number of B lymphocytes. This finding, we believe, is most
144 likely due to the increase in memory B-cells. Other studies either unchanged [18] or
145 increased numbers of B1 cells [25] in peripheral blood of HCV patients. This could
146 occur if the group included patients with systemic complications associated with the
147 dysregulation of B-cellular immunity. In the meantime, HCV patients demonstrated
148 a reduced number of less differentiated B-cell subsets (e.g., transitional and "naïve"
149 mature) and an increase in more differentiated (activated mature, "double negative"
150 B-cells). Our results demonstrate that chronic hepatitis C is associated with the
151 redistribution (or an imbalance) in B-cellular fractions towards more differentiated
152 cells.

153   CXCR3 expression is higher on more differentiated B-cell subsets, and our
154 findings on CXCR3 expression suggest that these B-cell subsets are attracted to the
155 infected liver tissues. Their presence in tissues and the degree of attraction varies:
156 resting memory B-cells, activated mature B-cells, less "double negative" B-cells,
157 and least CXCR3-expressing cells are transitional and "naïve" mature B-cells.

158   CXCR3 is involved in B lymphocyte transmigration through the endothelium
159 of sinusoidal capillaries of liver [4]. Our results on the expression of CXCR3 on B
160 lymphocytes and memory B-cells confirm already existing studies [14, 19].

161   Previously, we have published a review article on CXCR3 expression in
162 various infections, and although it focuses mostly on CXCR3 expression in T cells,
163 there are some points to be made concerning HCV [17]. For HCV infection, CXCL9,
164 CXCL10, and CXCL11 are key ligands for CXCR3 that are elevated [6]. The
165 persistent inflammation driven by CXCR3 ligands in HCV could influence B-cell
166 activation, antibody production, and possibly autoantibody formation. High serum

167 levels of CXCL10 are associated with advanced liver fibrosis and extrahepatic

168 manifestations like vasculitis and autoimmune thyroiditis in HCV patients [3].

169 CXCL10 levels correlate with liver fibrosis scores and enzyme concentrations,

170 suggesting a role in disease progression. Targeting CXCR3 or its ligands could be a

171 potential therapeutic approach to modulate B-cell responses in HCV.

172   We believe that B lymphocytes, specifically their more differentiated subsets,

173 are either constantly present, or migrate into the infected liver tissues during HCV

174 infection.

175 5 **Conclusions**

176   We discovered that CD38 and CXCR3 expression on B-cells is dependent on

177 viral load. In addition, we have demonstrated that the late stages of liver fibrosis are

178 followed by the depletion of memory cells and an upsurge in CXCR3+ B1 and B 2

179 cells. When taking HCV genotype into account, patients with HCV genotype 1

180 demonstrated higher levels of B2 subsets. These relationships require further

181 investigation and we encourage our readers and fellow colleagues to join the

182 research of this topic.

РИСУНКИ

Figure 1. A distribution of the main B cell subsets by expression levels of CD27/CD5 (A) and CD38/CD27 (B).

Рисунок 1. Распределение основных субпопуляций В-клеток на основании экспрессии CD27/CD5 (A) и CD38/CD27 (B).
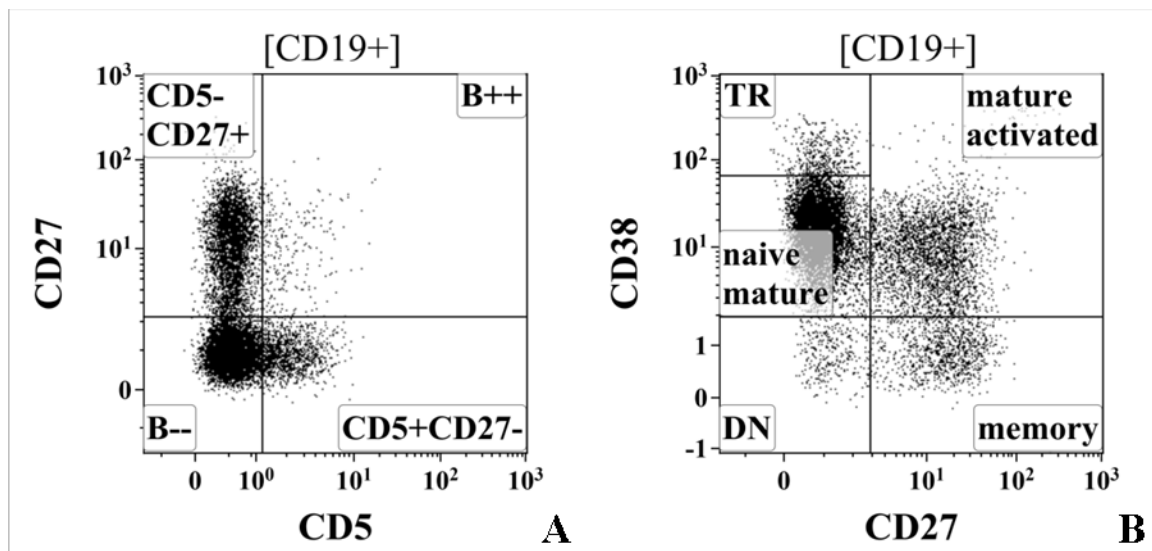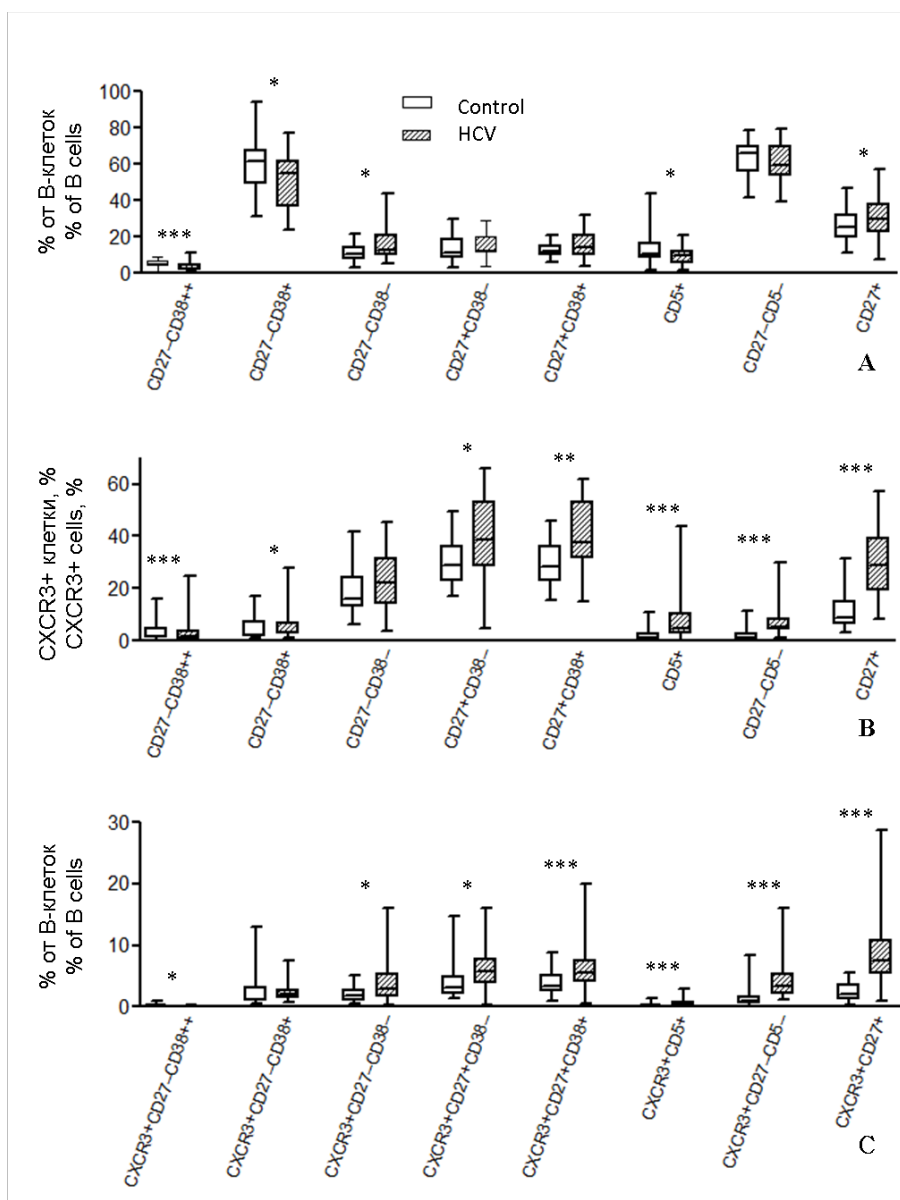
Figure 2. B lymphocyte subsets in peripheral blood of chronic HCV patients and healthy donors [Me (Q25 - Q75)].

Рисунок 2. Субпопуляции лимфоцитов периферической крови больных хроническим вирусным гепатитом С [Me (Q25 - Q75)].
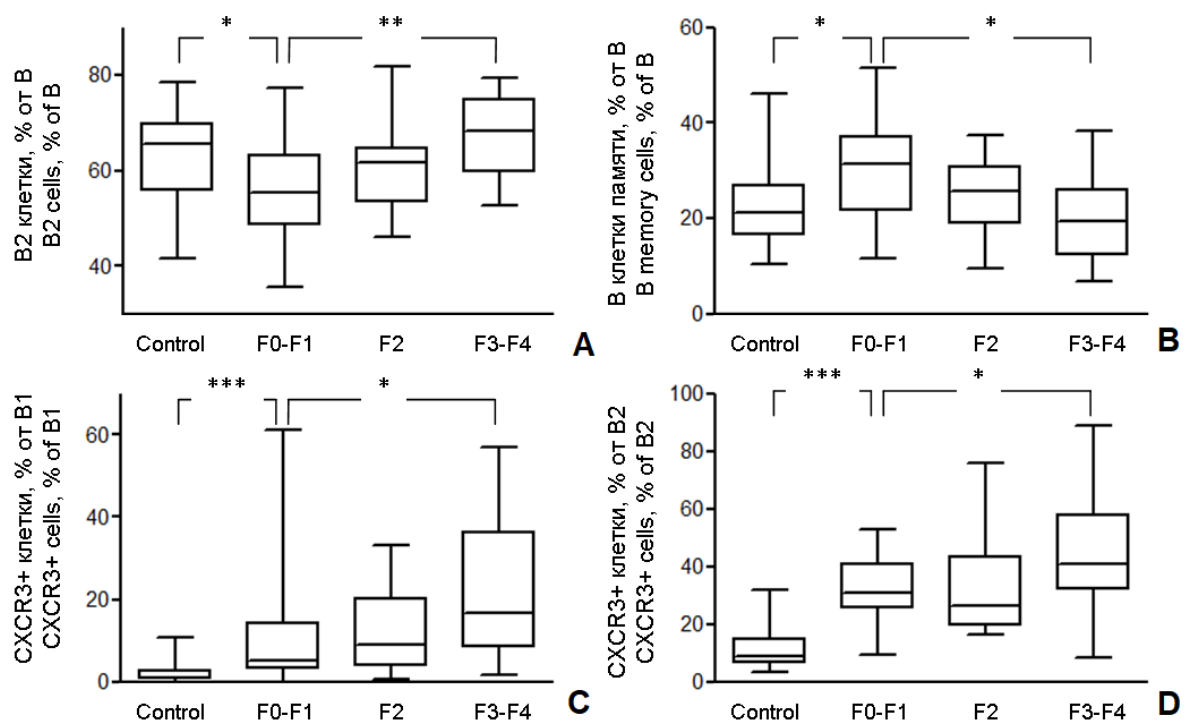

Comments. A: The percentage of B cell subsets of total B lymphocytes (CD19+); B: The percentage of CXCR3+ cells of B cell subsets; C: The percentage of CXCR3+ B cell subsets of total B lymphocytes (CD19+). * P < 0.05; ** P < 0.01; *** P < 0.001.

Комментарии. А: Процент В-клеточных субпопуляций от общего числа В-лимфоцитов (CD19+); В: Процент CXCR3+ клеток от В-клеточных субпопуляций; С: Процент CXCR3+ В-клеточных субпопуляций от общего числа В-лимфоцитов (CD19+). * P < 0,05; ** P < 0,01; *** P < 0,001.

Figure 3. The composition of lymphocyte subsets in peripheral blood of chronic HCV patients with various stages of fibrosis (F0-F1, F2, F3-F4) and healthy donors [Me (Q25 - Q75)].

Рисунок 3. Субпопуляционный состав лимфоцитов периферической крови больных хроническим вирусным гепатитом С с различными стадиями фиброза печени [Me (Q25 - Q75)].

Comments. A: The percentage of B2 cells (CD5–CD27–) of total B lymphocytes; B: The percentage of memory B cells (CD27+) of total B lymphocytes; C: The percentage of CXCR3+ B cell of B1 lymphocytes (CD5+CD19+); D: The percentage of CXCR3+ B cells of B2 lymphocytes (CD5– CD27–). * P < 0.05; **

P < 0.01; ******* P < 0.001; F0-F1, F2, F3-F4 - groups of HCV patients at different stages of liver fibrosis.

Комментарии. A: Процент В2-клеток (CD5–CD27–) от общего числа В-лимфоцитов; B: Процент В-клеток памяти (CD27+) от общего числа В-лимфоцитов; C: Процент CXCR3+ В-клеток от В1-лимфоцитов (CD5+CD19+); D: Процент CXCR3+ В-клеток от В2-лимфоцитов (CD5– CD27–). ***** P < 0,05; ****** P < 0,01; ******* P < 0,001; F0-F1, F2, F3-F4 – группы больных хроническим вирусным гепатитом С с различными стадиями фиброза печени.

ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

Блок 1. Информация об авторе ответственном за переписку

Арсентьева Наталья Александровна, к.б.н., старший научный сотрудник лаборатории молекулярной иммунологии, доцент кафедры иммунологии;

адрес: 197101, Россия, Санкт-Петербург, ул. Мира, 14.;

телефон: 89046465758;

e-mail: arsentieva_n.a@bk.ru

Arsentieva Natalia Alexandrovna, PhD in Biological sciences, senior researcher Laboratory of Molecular Immunology, associate professor of department of Immunology;

address: 14, ul. Mira, 197101, Saint Petersburg;

telephone: 89046465758;

e-mail: arsentieva_n.a@bk.ru

Блок 2. Информация об авторах

Елезов Дмитрий Сергееви, к.м.н., младший научный сотрудник лаборатории молекулярной иммунологии;

Elezov Dmitrii Sergeevich, PhD in Medicine sciences, Junior Researcher Laboratory of Molecular Immunology;

Кудрявцев Игорь Владимирович, к.б.н., заведующий лабораторией клеточной иммунологии, доцент кафедры иммунологии;

Kudryavtsev Igor Vladimirovich, PhD in Biological sciences, head of laboratory of cellular immunology, associate professor of department of Immunology;

Коробова Зоя Романовна, младший научный сотрудник лаборатории молекулярной иммунологии, ассистент кафедры иммунологии;

Korobova Zoya Romanovna, Junior Researcher Laboratory of Molecular Immunology, assistant professor of department of Immunology;

Тотолян Арег Артёмович, академик РАН, д.м.н., профессор, директор, заведующий кафедрой иммунологии;

Totolian Areg Artemovich, MD, PhD, professor, Academician of Russian Academy of Science, head of Saint Petersburg Pasteur Institute, chair of Department of Immunology.

Блок 3. Метаданные статьи

B-CELLS AND CXCR3+ EXPRESSION IN CHRONIC HEPATITIS C VIRUS INFECTION

СУБПОПУЛЯЦИИ В-И CXCR3+ В-КЛЕТОК ПЕРИФЕРИЧЕСКОЙ КРОВИ БОЛЬНЫХ ХРОНИЧЕСКИМ ВИРУСНЫМ ГЕПАТИТОМ С

Сокращенное название статьи для верхнего колонтитула:
B-CELLS IN HCV PATIENTS

В-КЛЕТКИ У БОЛЬНЫХ ГЕПАТИТОМ С

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количество таблиц – 0,

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СПИСОК ЛИТЕРАТУРЫ

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